Remarks

Claims 1, 5-9, 14, 20, 22-25, 27, 29, 35-39, 41, 42, 44-49, 51-53, 55-59, and 69-84 are pending. Claims 74, 76–82 were previously withdrawn. Claims 20, 22, and 23 have been amended.

Claims 20, 22, and 23 were amended to remove the term "about." These amendments are supported by the Specification, p. 15, ll. 4-7.

Claim Rejections Under 35 U.S.C. § 112

Claims 20, 22, and 23 were rejected under 35 U.S.C. § 112, second paragraph, as indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention. (Office Action, p. 3). Specifically, the Office Action alleges that claims 20, 22, and 23 are indefinite over the recitation of "no larger than about x nucleotides," and further alleges that "the extent of variance permitted by 'about' is unclear in this context." (Office Action, p. 3). Applicants have amended claims 20, 22, and 23 by removing the term "about." As such, Applicants submit that claims 20, 22, and 23 are sufficiently definite to satisfy the requirement of 35 U.S.C. § 112, second paragraph, and that "those skilled in the art would understand what is claimed when the claim is read in light of the specification." (*See Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1576 (Fed. Cir. 1986)). Therefore, Applicants respectfully request that the Examiner withdraw these rejections.

Claim Interpretation

The Office Action alleges that "totally random primers are also degenerate primers" (Office Action, p. 4). Applicants respectfully traverse this claim interpretation.

In the specification, Applicants independently define the terms "degenerate" and "random." While the Office Action correctly recites Applicants' definition of "degenerate," the Office Action incorrectly equates totally or completely random primers with degenerate primers. Specifically, degenerate primers are generated in view of the nucleotide sequence of the target molecule. Conversely, totally or completely random primers are generated without any consideration of the nucleotide sequence of the target molecule. For example, Applicants define degenerate primers as those "in which one or more of the nucleotide positions is occupied by more than one base." (Specification, p. 6, ll. 16-18). In other words, a degenerate primer can be likened to a specific primer in the sense that both degenerate and specific primers are designed in view of the nucleotide sequence of the target molecule. But, unlike a specific primer, a degenerate primer is not generated to be *completely* complementary to the target molecule.

Applicants provide a different definition for a random primer. "Random refers to an oligonucleotide in which each of the nucleotide positions is occupied by a base selected at random from among a complete set of possibilities, but commonly limited to the four nucleosides, dAMP, dCMP, dGMP, or dTMP." (emphasis added) (Specification, p. 6, ll. 23-26). Unlike a specific or degenerate primer, a random primer is generated ***without any consideration*** of the nucleotide sequence of the target molecule. Hence, the selection of a nucleotide at any particular position within the primer is totally or completely random. Therefore, the entire nucleotide sequence of the random primer is ***randomly selected***, and each position may be comprised of an A, T, G, or C.

Furthermore, when viewed in context, Applicants' claims distinguish degenerate primers from random primers. For example, in claim 1, Applicants claim "A process for ***selectively amplifying*** nucleic acid sequences comprising contacting ***multiple*** single-stranded non-circular ***degenerate*** oligonucleotide ***primers*** . . . ." (emphasis added). One skilled in the art would understand that degenerate primers rather than totally or completely random primers would ***selectively amplify*** the target nucleic acid sequence. One skilled in the art would also understand that the use of totally or completely random primers would result in the ***random amplification***, **BUT NOT** ***the selective amplification***, of the target nucleic acid sequence. Therefore, in light of this discussion, Applicants respectfully request the Examiner withdraw this interpretation and adopt an intrepretation of degenerate primers that is consistent with Applicants' disclosure and the art.

Rejections Under 35 U.S.C. § 102

Claims 1, 5-8, 14, 20, 22, 23, 25, 27, 35, 38, 51, 55-58, 69, 70, and 83 were rejected under 35 U.S.C. § 102(b) as being anticipated by Navarro *et al.* (*J. Virol. Meth.*, 1996, vol. 56, pp. 59-66), as evidenced by Kool (U.S. Pat. No. 6,096,880, Aug. 1, 2000) and Oyama *et al.* (*Anal. Biochem.*, 1988, vol. 172, pp. 444-450). (Office Action, p. 4). Applicants respectfully traverse these rejections.

Applicants first note that claims 5-8, 14, 20, 22, 23, 25, 27, 35, 38, 51, 55-58, 69, 70, and 83 all depend from claim 1 and therefore by definition encompass all the limitations of claim 1. Claim 1 is drawn to a process for ***selectively amplifying*** nucleic acid sequences. Specifically, claim 1 is drawn to a process for ***selectively amplifying*** nucleic acid sequences comprising, in

part, ***multiple*** single stranded non-circular ***degenerate*** oligonucleotide ***primers*** (P1), one or more single stranded amplification target circles (ATCs), a DNA polymerase, and multiple deoxynucleoside triphosphates (dNTPs). The claimed process of ***selective amplification*** occurs under conditions that promote the contacting of a plurality of P1 primers to each ATC. This process of ***selective amplification*** occurs via rolling circle replication of the ATC thereby ***forming multiple tandem sequence DNA*** (TS-DNA) products. (*See* claim 1).

Applicants also note that a "claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." (M.P.E.P § 2131 quoting *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987)). In the rejection of independent claim 1, the Office Action alleges that Navarro *et al.* teaches "a method of amplification comprising contacting multiple single stranded non-circular degenerate oligonucleotide primers (P1), one or more single stranded amplification target circles (ATCs), a DNA polymerase and multiple deoxynucleotide triphosphates (dNTPs) . . . ." (See Office Action, p. 5). But, by the Office Action's own admission, Navarro *et al.* does not "specifically teach that TS-DNA is obtained in the first step of the viral circles amplification." (Office Action, p. 5). Hence, the Office Action's rejection is not consistent with the requirement that each and every element of Applicants' claim exists in a single reference. For at least this reason, Navarro *et al.* fails to anticipate claims 1, 5-8, 14, 20, 22, 23, 25, 27, 35, 38, 51, 55-58, 69, 70, and 83.

Applicants also submit that Navarro *et al.* fails to teach the use of ***multiple degenerate primers*** and ***selective amplification*** of a nucleic acid sequence as claimed by Applicants. For

example, during the initial reverse transcription (RT) reaction in Method 1, Navarro *et al.* employs ***completely random hexamer primers*** to generate cDNA. (p. 60, ¶ 6). Navarro *et al.* chooses completely random primers because the nucleotide sequence of the small circular RNA is unknown. In other words, Navarro *et al.* requires completely random primers of unknown nucleotide sequence because the nucleotide sequence of the target molecule to which the primers hybridize is likewise unknown. Similarly, in Method 2, Navarro *et al.* employs a 26-mer comprised of 6 completely random nucleotides at the 3' end. As Figure 1 illustrates, these 6 completely random nucleotides at the 3' end of the primer hybridize to a completely random portion of the target molecule. Hence, in Navarro *et al.*, the amplification is random amplification NOT selective amplification. In other words, Navarro et al. fails to disclose ***selective amplification*** of the target molecule because everything in the Navarro et al. reactions is random. The same is illustrated by Navarro et al. in that the ***completely random primers*** hybridize to the target molecule and amplify ***completely random portions*** of the target molecule. Thus, Navarro *et al.* teaches the use of ***random primers*** for ***non-specific*** or ***non-selective amplification*** and fails to teach the use of ***degenerate primers*** for ***selective amplification*** of a nucleic acid sequence.

In addition, Applicants note that "normally, only one reference should be used in making a rejection under 35 U.S.C. 102." (M.P.E.P. § 2131.01). The M.P.E.P. recognizes only three exceptions to this rule: (1) to prove the primary reference contains an "enabled disclosure;" (2) to explain the meaning of a term used in the primary reference; and (3) to show that a characteristic not disclosed in the reference is inherent. None of these three exceptions applies to the current

set of circumstances. Regarding the first exception, Kool and Oyama *et al.* do not prove that Navarro *et al.* contains an "enabled disclosure." Regarding the second exception, Kool and Oyama *et al.* do not explain the meaning of a term used in Navarro *et al.* Regarding the third exception, Kool and Oyama *et al.* do not demonstrate that a characteristic not disclosed in Navarro *et al.* is inherent. It appears that the Office Action is relying on exception number 3, based on the final lines of page 5, however the mere fact that Kool teaches amplification of small circular DNA or RNA molecules in the presence of a primer and polymerase, does not lend it self to a similar defacto inherent teaching by Navarro *et al.*

In an attempt to circumvent (1) the Office Action's admission that Navarro *et al.*'s failure to teach TS-DNA, (2) the M.P.E.P's requirement that each and every element of the claim must be found in a single reference, and (3) the M.P.E.P.'s prohibition against using multiple references to make a 35 U.S.C. § 102 rejection, the Office Action alleges that Kool teaches "amplification of small circular DNA or RNA molecules in the range of 15 to 15,000 nucleotides in the presence of a primer and a DNA polymerase results in production of multiple copies of the circular target by rolling circle synthesis." (Office Action, p. 5). The Office Action also alleges that "by teaching amplification of circular RNA targets using these two polymerase Navarro et al. ***inherently teach*** formation of multimeric copies of the single-stranded circles." (emphasis added) (Office Action, p. 5).

In Response, Applicants note that "the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." (M.P.E.P. §

2112(IV) quoting *Ex parte Levy,* 17 U.S.P.Q. 2d 1461, 1464 (Bd. Pat. App. & Inter. 1990)). "The mere fact that a certain thing may result from a given set of circumstances is not sufficient . . . the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill.'" (*In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999)). As Navarro *et al.* teaches the use of ***completely random primers*** in the ***random amplification*** of a target molecule with an ***unknown nucleotide sequence***, the Office Action fails to meet the burden of proof regarding the allegation of inherency.

It is well established that in making a rejection under 35 U.S.C. § 102, the USPTO has the burden of establishing that the cited reference teaches each and every limitation of the claims. As described above, Applicants submit that the Office Action fails to meet this burden. In particular, the Examiner fails to direct Applicants' attention to any portion of Navarro *et al.* that teaches Applicants' claimed method of ***selectively amplifying*** nucleic acid sequences by generating TS-DNA through rolling circle replication of one or more ATCs using ***multiple degenerate primers***. Similarly, Kool and Oyama *et al.*, which the Office Action cites for allegedly teaching that the "AMV reverse transcriptase does not have the 3' → 5' exonuclease activity," and then only cites Oyama *et al.* in the context of a rejection of a dependent claim, do not supplement the elements missing from the primary reference - Navarro *et al.* Consequently, these references fail to anticipate independent claim 1, and therefore, fail to anticipate dependent claims 5-8, 14, 20, 22, 23, 25, 27, 35, 38, 51, 55-58, 69, 70, and 83. Applicants respectfully request that the Examiner withdraw these rejections.

For all the reasons stated above, Applicants respectfully submit that Navarro *et al.* fails to teach all the claimed elements. Therefore, Applicant's submit that Navarro *et al.* fails to anticipate independent claim 1, and therefore, fails to anticipate dependent claims 5-8, 14, 20, 22, 23, 25, 27, 35, 38, 51, 55-58, 69, 70, and 83. As such, Applicants respectfully request that the Examiner withdraw these rejections.

Claim Rejections Under 35 U.S.C. § 103

1. Claim 9 was rejected under 35 U.S.C. § 103(a) as obvious over Navarro *et al.*, as evidenced by Kool and Oyama *et al.* (Office Action, p. 7). Applicants respectfully traverse this rejection.

Applicants first note that claim 9 depends from claim 1, and therefore by definition comprises all of the limitations of claim 1. Secondly, it appears to Applicants that the Office Action cites the primary reference, Navarro *et al.*, in the same way and for the same disclosures for which the Office Action previously applied Navarro *et al.* in the 35 U.S.C. § 102 rejection discussed above. For at least the reasons discussed above in connection with the rejection under 35 U.S.C. § 102, Navarro *et al.* fails to disclose or suggest every limitation of claim 1. Specifically. Navarro *et al.* fails to disclose or suggest teach the use of ***degenerate primers*** for ***selective amplification*** of a nucleic acid sequence.

In addition, the Office Action admits that "Navarro et al. teach using hexamer primers, but do not teach octamers." (Office Action, p. 7). However, the Office Action alleges that "it would have been obvious to one of ordinary skill in the art to have used any primer length

appropriate for the experiment." (Office Action, p. 7). The Office Action further alleges that routine optimization is not considered inventive, and that "no evidence has been presented that the selection of specific primer length was other than routine, that the products resulting from the use of specific primer lengths have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art." (Office Action, p. 7).

As discussed above, Navarro *et al.* fails to teach or suggest every feature of Applicants' claimed process of ***selectively amplifying*** nucleic acid sequences by generating TS-DNA through rolling circle replication of one or more ATCs using ***multiple degenerate primers***. Rather, Navarro *et al.* teaches the use of ***completely random primers*** in the ***random amplification*** of a target molecule with an ***unknown nucleotide sequence***.

In an attempt to circumvent the lack of teaching or suggestion of the aforementioned elements missing from Navarro *et al.*, the Office Action cites Kool and Oyama *et al.* It appears to Applicants that the Office Action is applying Kool and Oyama *et al.* in the same way and for the same disclosures for which the Office Action previously applied Kool and Oyama *et al.* in the 35 U.S.C. § 102 rejection discussed above. However, in the current 35 U.S.C. § 103 rejection, the Office Action fails to specifically cite Kool and Oyama *et al.* for any particular alleged teaching. Applicants first submit that such an omission fails to comply with M.P.E.P. § 2142, which states that the "key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious." More recently, the United States Supreme Court noted that the analysis supporting a rejection under 35 U.S.C. § 103 should be made explicit. (*KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727

(2007)). Because the Office Action omits any specific discussion of Kool and Oyama *et al.* in this 35 U.S.C. § 103 rejection, the Office Action fails to meet its burden.

Notwithstanding the Office Action's failure to meet its burden and in the interest of being complete, Applicants will address the alleged teachings of Kool and Oyama *et al.* In the 35 U.S.C. § 102 rejection, the Office Action alleged that Kool teaches (1) "amplification of small circular DNA or RNA molecules in the range of 15 to 15,000 nucleotides in the presence of a primer and a DNA polymerase results in production of multiple copies of the circular target by rolling circle synthesis," and (2) "that polymerases useful in the amplification process include Klenow fragment of DNA polymerase I and AMV reverse transcriptase." (Office Action, p. 5). Also in the 35 U.S.C. § 102 rejection, the Office Action allege that Oyama *et al.* teaches that "AMV reverse transcriptase does not have 3' → 5' exonuclease activity." (Office Action, p. 6).

Even if the Office Action intended to cite Kool and Oyama *et al.* for the same alleged teachings for which the Office Action offered Kool and Oyama *et al.* in the 35 U.S.C. § 102 rejection, both references fail to teach or suggest ***selectively amplifying*** nucleic acid sequences using ***multiple degenerate primers***. Hence, both Kool and Oyama *et al.* fail to supplement the elements missing from Navarro *et al.* For at least these reasons, either individually or in combination, Navarro *et al.*, Kool, and Oyama *et al.* fail to teach or suggest every feature of independent claim 1, and therefore fail to make obvious dependent claim 9. Applicants respectfully request that the Examiner withdraw this rejection.

2. Claims 29, 38, 39, 41, 42, 44-47, and 59 were rejected under 35 U.S.C. § 103(a) as obvious over Navarro *et al.*, as evidenced by Kool and Oyama *et al.*, and Skerra (*Nucl. Acids*

Res., 1992, vol. 20, pp. 3551-3554) (Office Action, pp. 7-8). Applicants respectfully traverse these rejections.

Applicants first note that claims 29, 38, 39, 41, 42, 44-47, and 59 depend from claim 1 and therefore, by definition, comprise all of the limitations of claim 1. Secondly, it appears to Applicants that the Office Action cites the primary reference, Navarro *et al.*, in the same way and for the same disclosures for which the Office Action previously applied Navarro *et al.* in the 35 U.S.C. § 102 rejection discussed above. For at least the reasons discussed above in connection with the rejection under 35 U.S.C. § 102, Navarro *et al.* fails to disclose or suggest every limitation of claim 1. Specifically, Navarro *et al.* fails to disclose or suggest teach the use of ***degenerate primers*** for ***selective amplification*** of a nucleic acid sequence.

In addition, the Office Action admits that Navarro *et al.* fails to teach "using exonuclease-resistant primers or primers with phosphorothioate nucleotides," but alleges that Navarro *et al.* teaches "Klenow fragment DNA of polymerase I and DNA polymerase I." (Office Action, p. 8). The Office Action also alleges that Skerra teaches (1) "that incorporation of phosphorothioate nucleotides into primers protects them from degradation by the 3'→ 5' exonuclease activity of DNA polymerases," (2) that "incorporation of phoshorothioate nucleotides into primers at the 3'-end, making them resistant to exonuclease activity," (3) "mixtures of primers resistant to exonuclease activity and not reseistant to exonuclease activity and primers resistant to exonuclease activity," and (4) "3' → 5' exonuclease activity due to DNA polymerase." (Office Action, p. 8). The Office Action also alleges that "it would have been prima facie obvious to one

of ordinary skill in the art at the time of the invention to have used the exonuclease-resistant primers of Skerra in the method of Navarro et al." (Office Action, p. 8).

As discussed above, Navarro *et al.* does not teach or suggest every feature of Applicants' claimed method of ***selectively amplifying*** nucleic acid sequences by generating TS-DNA through rolling circle replication of one or more ATCs using ***multiple degenerate primers***. Rather, Navarro *et al.* teaches the use of ***completely random primers*** in the ***random amplification*** of a target molecule with an ***unknown nucleotide sequence.***

In an attempt to circumvent the lack of teaching or suggestion of the aforementioned elements missing from Navarro *et al.*, the Office Action cites Kool and Oyama *et al.* Applicants note that the Office Action again fails to specifically cite Kool and Oyama *et al.* for any particular alleged teaching. Because the Office Action omits any specific discussion of Kool or Oyama *et al.* in this 35 U.S.C. § 103 rejection, the Office Action fails to meet its burden. Nevertheless, both references fail to teach or suggest ***selectively amplifying*** nucleic acid sequences using ***multiple degenerate primers***, and fail to supplement the elements missing from the primary reference - Navarro *et al.*

Furthermore, Skerra which is cited for teaching that the incorporation of phosphorothioate nucleotides into primers protects them from degredation by the 3'→ 5' exonuclease activity of DNA polymerses fails to supplement the missing elements from Navarro *et al.*, Kool, and Oyama *et al.* Each of the cited references, Navarro *et al.*, Kool, Oyama *et al.*, and Skerra fail to teach or suggest ***selectively amplifying*** nucleic acid sequences using ***multiple degenerate primers***. Thus, Navarro *et al.*, Kool, Oyama *et al.*, and Skerra either alone or in

combination, fail to disclose or suggest each and every element of claims 29, 38, 39, 41, 42, 44-47 and 59. Accordingly, Navarro *et al.*, Kool, Oyama *et al.*, and Skerra do not make obvious claims 29, 38, 39, 41, 42, 44-47 and 59. Applicants respectfully request withdrawal of this rejection.

3. Claims 35, 38, 44, 48, and 49 were rejected under 35 U.S.C. § 103(a) as obvious over Navarro *et al.*, as evidenced by Kool and Oyama *et al.*, and Ott *et al.* (*Biochemistry*, 1987, vol. 26, pp. 8237-8241). (Office Action, p. 9). Applicants respectfully traverse these rejections.

Applicants first note that claims 35, 38, 44, 48, and 49 depend from claim 1 and therefore, by definition, comprise all of the limitations of claim 1. Secondly, it appears to Applicants that the Office Action cites the primary reference, Navarro *et al.*, in the same way and for the same disclosures for which the Office Action previously applied Navarro *et al.* in the rejection under 35 U.S.C. § 102 discussed above. For at least the reasons discussed above in connection with the rejection under 35 U.S.C. § 102, Navarro et al. fails to disclose or suggest every limitation of claim 1. Specifically, Navarro *et al.* fails to disclose or suggest teach the use of ***degenerate primers*** for ***selective amplification*** of a nucleic acid sequence.

The Office Action admits that Navarro *et al.* fails to teach "using exonuclease-resistant primers or primers with phosphorothioate nucleotides," but alleges that Navarro *et al.* teaches "DNA polymerase 1, T4 DNA polymerase and Taq DNA polymerase."(Office Action, p. 9). The Office Action cites Ott *et al.* for allegedly teaching (1) "the protection of oligonucleotide primers from the 5'→ 3' exonuclease activity," (2) the "incorporation of phosphorothioate nucleotides into 5'-ends of the primers to make the exonuclease resistant," and (3) the "incorporation of

more than one phosphorothioate nucleotides into the primer." (Office Action, p. 9). The Office Action further alleges that "[i]t would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to have used the phosphorothioate nucleotides of Ott et al. in the primers of Navarro et al." (Office Action, p. 10).

As discussed above, Navarro *et al.* does not teach or suggest every feature of Applicants' claimed method of ***selectively amplifying*** nucleic acid sequences by generating TS-DNA through rolling circle replication of one or more ATCs using ***multiple degenerate primers***. Rather, Navarro *et al.* teaches the use of ***completely random primers*** in the ***random amplification*** of a target molecule with an ***unknown nucleotide sequence.***

In an attempt to circumvent the lack of teaching or suggestion of the aforementioned elements missing from Navarro *et al.*, the Office Action cites Kool and Oyama *et al.* Applicants note that the Office Action again fails to specifically cite Kool and or Oyama *et al.* for any particular alleged teaching. Because the Office Action omits any specific discussion of Kool or Oyama *et al.* in this 35 U.S.C. § 103 rejection, the Office Action fails to meet its burden. Nevertheless, both references fail to teach or suggest ***selectively amplifying*** nucleic acid sequences using ***multiple degenerate primers***, and fail to supplement the elements missing from the primary reference - Navarro *et al.*

Furthermore, Ott *et al.* which is cited for teaching incorporation of phosphothioate nucleotides into 5'-ends of the primers t make them exonuclease resistant fails to supplement the missing elements from Navarro *et al.*, Kool and Oyama *et al.* Each of the cited references, Navarro *et al.*, Kool, Oyama *et al.*, and Ott *et al.* fail to disclose or suggest ***selectively amplifying***

nucleic acid sequences using ***multiple degenerate primers***. Thus, Navarro *et al.*, Kool, Oyama *et al.*, and Ott *et al.*, either alone or in combination, fail to teach or suggest each and every element of claims 29, 38, 39, 41, 42, 44-47 and 59. Accordingly, Navarro *et al.*, Kool, Oyama *et al.*, and Ott *et* al. do not make obvious claims 29, 38, 39, 41, 42, 44-47 and 59. Applicants respectfully request withdrawal of this rejection.

4. Claims 1, 5-9, 14, 20, 22-25, 27, 35, 38, 51, 55-58, 69-71, 75, and 83 were rejected under 35 U.S.C. § 103(a) as obvious over Kool and Navarro *et al.*, as evidenced by Oyama *et al.* (Office Action, p. 10). Applicants respectfully traverse these rejections.

Applicants first note that claims 5-9, 14, 20, 22-25, 27, 35, 38, 51-58, 69-71, 75, and 83 depend from claim 1 and therefore, by definition, comprise all of the limitations of claim 1.

Applicants note that before a reference or a combination of references make obvious a claim or claims, "[f]irst, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations." (M.P.E.P. § 2143)

For several reasons, the combination of Kool and Navarro *et al.* fail to make obvious independent claim 1, and therefore, fail to make obvious dependent claims 5-9, 14, 20, 22-25, 27, 35, 38, 51, 55-58, 69-71, 75, and 83. First, the Office Action admits that Kool fails to teach the use of multiple degenerate primers. Second, both Kool and Navarro *et al.* fails to teach or suggest every feature of Applicants' claimed process. Specifically, both references fail to teach

or suggest ***selectively amplifying*** nucleic acid sequences using ***multiple degenerate primers***. Third, the cited portions of Oyama *et al.* fails to supplement the missing elements from Kool and Navarro *et al.* Fourth, and contrary to the Office Action's allegations, there is no motivation to combine the methods of Navarro *et al.* and Kool.

First, regarding Applicants' independent claim 1, the Office Action alleges that "[i]t would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to have used multiple degenerate primers of Navarro et al. in the method of amplification of circular nucleic acid targets of Kool with a reasonable expectation of success." (Office Action, p. 13). However, the Office Action admits that "Kool does not teach using multiple degenerate primers," and therefore, the Office Action relies on Navarro *et al.* for its alleged teaching of multiple degenerate primers. (Office Action, p. 11). As described above, Navarro et al. teaches the use of ***completely random primers*** in the ***random amplification*** of a target molecule with an ***unknown nucleotide sequence***. Navarro *et al.* fails to teach the claimed method of ***selectively amplifying*** nucleic acid sequences by generating TS-DNA through rolling circle replication of one or more ATCs using ***multiple degenerate primers***. In other words, Navarro *et al.* teaches the use of ***random primers*** for ***non-specific*** or ***non-selective amplification*** and fails to teach the use of ***degenerate primers*** for ***selective amplification*** of a nucleic acid sequence.

Second, in an attempt to supplement the elements missing from the primary reference - Kool, the Office Action cites Navarro *et al.* for allegedly teaching "a method of amplification comprising contacing multiple single stranded non-circular degenerate oligonucleotide primers

(P1), one or more single stranded amplification target circles (ATCs), a DNA polymerase and multiple deoxynucleoside triphosphates (dNTPs) . . . ." (Office Action, p. 11). The Office Action alleges that "it would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to have used multiple degenerate primers of Navarro et al. in the method of amplification of circular nucleic acid targets of Kool with a reasonable expectation of success." (Office Action, p. 13). According to the Office Action, the "motivation to do so, provided by Navarro et al., would have been that using degenerate primers allowed amplification of targets with unknown sequences and their cloning using minimum amounts of starting RNA." (Office Action, p. 13).

Again, as discussed above, Navarro *et al.* fails to teach or suggest every feature of Applicants' claimed process. Specifically, Navarro *et al.* fails to teach or suggest ***selectively amplifying*** nucleic acid sequences using ***multiple degenerate primers***. Rather, Navarro *et al.* teaches the use of ***completely random primers*** in the ***random amplification*** of a target molecule with an ***unknown nucleotide sequence.*** Hence, Navarro *et al.* fails to supplement the elements missing from Kool.

Third, the Office Action ***only*** cites Oyama *et al.* in the rejection of dependent claims. Furthermore, as described above, the cited portions of Oyama *et al.* fail to teach or suggest ***selectively amplifying*** nucleic acid sequences using ***multiple degenerate primer***, and therefore, Oyama *et al.* fails to supplement the elements missing from both Navarro *et al.* and the primary reference - Kool.

Fourth, and contrary to the Office Action's allegations, there is no motivation to combine the methods of Navarro *et al.* and Kool. For example, Navarro *et al.* concerns PCR approaches for "small circular RNAs of unknown sequence." (Navarro *et al.*, p. 64, ¶ 4). Throughout Navarro *et al.*, the methods and the subsequent teachings refer ***only*** to ***random primers*** and ***random amplification***. For instance, Navarro *et al.* admits that they "have developed these approaches by adapting two random-PCR methods proposed recently to construct whole cDNA libraries." (Navarro *et al.*, p. 64, ¶ 4). Furthermore, Navarro *et al.* teaches that "when there is ***no prior sequence information*** of the RNA to be cloned, the case for which the methodology *here reported* has been developed, a radioactive cDNA probe must be synthesized using reverse transcriptase and *random primers*." (emphasis added) (Navarro *et al.*, p. 65, ¶ 1). As Navarro *et al.* explains, their methods specifically use random primers to "avoid introducing any assumption about the RNA sequence." (Navarro *et al.*, p. 59, ¶1). These passages indicate that Navarro *et al.* does not concern the ***selective amplification*** of a target molecule using ***multiple degenerate primers***. Rather, Navarro *et al.* concerns the use of ***completely random primers*** in the ***random amplification*** of a target molecule with an ***unknown nucleotide sequence.***

On the other hand, Kool teaches that their "amplified run-on synthesis produces a long single multimer strand which is made up of many end-to-end copies of the nucleotide sequence complementary to the circular template sequence, and contains multiple copies of the desired oligonucleotide product." (Kool, col. 13, ll. 5-9). In other words, the methods of Kool are directed to the large-scale synthesis of a ***desired*** oligomer with a ***specific*** known nucleotide sequence using ***specific primers*** of a known nucleotide sequence. Therefore, the single-stranded

circular template is ***necessarily complementary*** to the nucleotide sequence of the ***desired*** oligonucleotide product. (*See* Kool, col. 5, ll. 51-53). Unlike Navarro *et al.*, the methods of Kool ***require*** prior information regarding the nucleotide sequence of the template. Consequently, Kool employs a ***singular primer*** with a ***predetermined nucleotide sequence and length***. For instance, in each example that utilizes a primer, Kool teaches (1) a synthesized circular target of known nucleotide sequence, and (2) a primer of known nucleotide sequence, which is complementary to the nucleotide sequence of the circular target. (Kool, *see* Examples 1, 2, 3, 4, 6, 8, 12, 13, 14, 15, and 17).

Because Kool aims for the massive production of a desired oligomer of ***known nucleotide sequence***, Kool teaches ***specific primers*** of known nucleotide sequence. This is directly at odds with Navarro *et al.* In other words, the two methods of Kool and Navarro *et al.* are different in both the compositions used as well as the goals sought to be obtained. Hence, Applicants submit that one of skill in the art would not have been motivated to combine the references of Kool and Navarro *et al*. Furthermore, one skilled in the art would have recognized that implementing into the methods of Kool the completely random hexamer primer approach of Navarro *et al*. would be ***counterproductive***. In Kool, the use of a primer ***specific*** for the nucleotide sequence of target molecule is the most efficient way to produce an oligomer with a ***specifically desired*** nucleotide sequence. Substituting into the methods of Kool the completely random hexamer primer approach of Navarro *et al.* would not provide **a reasonable expectation of success** in achieving Kool's goals. Furthermore, the random hexamer primer approach of

Navarro *et al.* would be **less efficient** (if applicable at all) than the specific primer approach already employed by Kool.

Moreover, to implement into the methods of Kool the completely random hexamer primer approach of Navarro *et al.* would alter Kool's ***fundamental principle of the operation***. It is well established that if the proposed modification or combination would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. ((*In re Ratti*, 270 F.2d 810 (C.C.P.A. 1959)). Kool aims to produce large quantities of a desired oligomer product of ***known nucleotide sequence***. Therefore, Kool employs a circular template of ***known nucleotide sequence*** and a complementary primer (also with a ***known nucleotide sequence***). Here, using the completely random hexamer primer approach of Navarro *et al.* would render the methods of Kool unsatisfactory for the intended purpose of producing large quantities of a desired oligomer product with a known nucleotide sequence. Rather, using the completely random hexamer primer approach of Navarro *et al.* in the methods of Kool would produce numerous ***undesired*** and ***randomly generated*** oligomer products. As the Federal Circuit explained, "If a proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification." (*In re Gordon*, 733 F.2d 900 (Fed. Cir. 1984)).

For all the reasons above, Applicants submit that the Office Action fails to meet the burden of this three-part obviousness test. First, the Office Action fails to direct Applicants' attention to portions of the cited references that teach or suggest to one skilled in the art that the

methods of Kool and Navarro *et al.* should be modified or combined. Second, the Office Action fails to demonstrate how the alleged teachings of Navarro *et al.*, if incorporated into the methods of Kool, would provide a reasonable expectation of success in achieving Kool's goals. Third, either individually or in combination with one another, Kool, Navarro *et al.*, and Oyama *et al.* fail to teach or suggest every feature of the claims. Therefore, these references fail to make obvious independent claim 1, and also fail to make obvious dependent claims 5-9, 14, 20, 22-25, 27, 35, 38, 51-58, 69-71, 75, and 83. Applicants respectfully request that the Examiner withdraw these rejections.

5. Claims 29, 35-39, 44, 45, 49, 49, and 51-53 were rejected under 35 U.S.C. § 103(a) as obvious over Kool and Navarro *et al.* (as evidenced by Oyama *et al.*) as applied to claim 1, and further in view of Lizardi (U.S. Pat. No. 5,854,033) and Blanco *et al.* (*J. Biol. Chem.*, 1989, 264: 8935-8940). Applicants respectfully traverse these rejections.

Applicants first note that claims 29, 35-39, 44, 45, 49, 49, and 51-53 depend from claim 1 and therefore, by definition, comprise all of the limitations of claim 1. Applicants also note that the Office Action applies Kool, Navarro *et al.*, and Oyama *et al.* in the same way and for the same disclosure for which Kool, Navarro *et al.*, and Oyama *et al.* was applied in the rejection above under 35 U.S.C. § 103.

For at least the reasons discussed above in connection with the rejection under 35 U.S.C. § 103, Kool, Navarro *et al.*, and Oyama *et al.* fails to disclose or suggest every limitation of claims 1. Specifically, Kool, Navarro *et al.*, and Oyama *et al.* fail to teach or suggest ***selectively***

amplifying nucleic acid sequences using ***multiple degenerate primers*** and contrary to the Office Action's allegations, there is no motivation to combine the methods of Navarro *et al.* and Kool.

Lizardi, which was cited for teaching rolling circle amplification of circular targets, and Blanco *et al.*, which was cited to provide the motivation to combine Lizardi with Kool and Navarro *et al.*, fail to supplement the missing elements from Kool, Navarro *et al.*, and Oyama *et al.* Kool, Navarro *et al.*, Oyama *et al.*, Lizardi, and Blanco *et al.* fail to teach or suggest ***selectively amplifying*** nucleic acid sequences using ***multiple degenerate primers***.

Thus, Kool, Navarro *et al.*, Oyama *et al.,* Lizardi, and Blanco *et al.*, either alone or in combination, fail to disclose or suggest each and every element of claims 29, 35-39, 44, 45, 49, 49, and 51-53. Accordingly, Kool, Navarro *et al.*, Oyama *et al*, Lizardi., and Blanco *et al.* do not make obvious claims 29, 35-39, 44, 45, 49, 49, and 51-53. Applicants respectfully request withdrawal of these rejections.

6. Under 35 U.S.C. § 103(a), the Office Action rejects as obvious claims 29, 35, 38, 39, 41, 42, 44-47, and 59 over Kool and Navarro *et al.* (as evidenced by Oyama *et al.*), as applied to claim 1 above, and further in view of Skerra. (Office Action, p. 16). Applicants respectfully traverse these rejections.

Applicants first note that claims 29, 35, 38, 39, 41, 42, 44-47, and 59 depend from claim 1 and therefore, by definition, comprise all of the limitations of claim 1. Applicants also note that the Office Action applies Kool, Navarro *et al.*, and Oyama *et al.* in the same way and for the same disclosure for which Kool, Navarro *et al.*, and Oyama *et al.* was applied in the rejection above under 35 U.S.C. § 103. For at least the reasons discussed above in connection with the

rejection under 35 U.S.C. § 103, Kool, Navarro *et al.*, and Oyama *et al.* fails to disclose or suggest every limitation of claims 1. Specifically, Kool, Navarro *et al.*, and Oyama *et al.* fail to teach or suggest ***selectively amplifying*** nucleic acid sequences using ***multiple degenerate primers*** and contrary to the Office Action's allegations, there is no motivation to combine the methods of Navarro *et al.* and Kool.

Furthermore, as discussed above, the combination of Kool, Navarro *et al.*, and Oyama *et al.* fail to make obvious independent claim 1, and therefore, also fail to make obvious dependent claims 29, 35, 38, 39, 41, 42, 44-47, and 59. To reiterate, (1) the Office Action admits that Kool fails to teach the use of multiple degenerate primers; (2) Navarro *et al.* fails to teach or suggest every feature of Applicants' claimed process including ***selective amplification*** of target nucleic acid sequences using ***multiple degenerate primers***, (3) the cited portions of Oyama *et al.* fail to teach or suggest every feature of Applicants' claimed process, and therefore fail to supplement the elements missing from Navarro *et al.* and Kool, and (4) contrary to the Office Action's allegations, there is no motivation to combine the methods of Navarro *et al.* and Kool.

Skerra which is cited for teaching that the incorporation of phosphorothioate nucleotides into primers protects them from degradation by the 3'→ 5' exonuclease activity of DNA polymerase fails to supplement the missing elements from Navarro *et al.*, Kool and Oyama *et al.* Each of the cited references, Navarro *et al.*, Kool, Oyama *et al.*, and Skerra fail to teach or suggest ***selectively amplifying*** nucleic acid sequences using ***multiple degenerate primers***. Thus, Navarro *et al.*, Kool, Oyama *et al.*, and Skerra, either alone or in combination, fail to disclose or suggest each and every element of claims 29, 35, 38, 39, 41, 42, 44-47, and 59. Accordingly,

Navarro *et al.*, Kool, Oyama *et al.* and Skerra do not make obvious claims 29, 35, 38, 39, 41, 42, 44-47, and 59. Applicants respectfully request withdrawal of these rejections.

7. Claims 72 and 73 were rejected under 35 U.S.C. § 103(a) as obvious over Kool and Navarro *et al.* (as evidenced by Oyama *et al.*) as applied to claims 1 and 71, and further in view of Waggoner *et al.* (U.S. Patent No. 5,268,486, Dec. 7, 1993). Applicants respectfully traverse these rejections.

Applicants first note that claims 72 and 73 depend from claim 1 and therefore, by definition, comprise all of the limitations of claim 1. Applicants also note that the Office Action applies Kool, Navarro *et al.*, and Oyama *et al.* in the same way and for the same disclosure for which Kool, Navarro *et al.*, and Oyama *et al.* was applied in the rejection above under 35 U.S.C. § 103. For at least the reasons discussed above in connection with the rejection under 35 U.S.C. § 103, Kool, Navarro *et al.*, and Oyama *et al.* fails to disclose or suggest every limitation of claims 1. Specifically, Kool, Navarro *et al.*, and Oyama *et al.* fail to teach or suggest ***selectively amplifying*** nucleic acid sequences using ***multiple degenerate primers*** and contrary to the Office Action's allegations, there is no motivation to combine the methods of Navarro *et al.* and Kool.

Furthermore, while the Office Action admits that Kool fails to teach cyanine dies, the Office Action alleges that Waggoner *et al.* teaches cyanine fluorescent dyes. (Office Action, p. 18). As discussed above, the combination of Kool, Navarro *et al.*, and Oyama *et al.* fail to make obvious independent claim 1, and therefore, also fail to make obvious dependent claims 72 and 73. To reiterate, (1) the Office Action admits that Kool fails to teach the use of multiple degenerate primers; (2) Navarro *et al.* fails to teach or suggest every feature of Applicants' claimed process including ***selective amplification*** of target nucleic acid sequences using ***multiple degenerate primers***, (3) the cited portions of Oyama *et al.* do not teach or suggest every feature of Applicants' claimed process, and therefore fail to supplement the elements missing from Navarro *et al.* and Kool, and (4) contrary to the Office Action's allegations, there is no motivation to combine the methods of Navarro *et al.* and Kool.

Waggoner et al. which is cited for teaching cyanine fluorescent dyes fails to supplement the missing elements from Navarro *et al.*, Kool, and Oyama *et al.* Each of the cited references, Navarro *et al.*, Kool, Oyama *et al.*, and Waggoner *et al.* fail to teach or suggest ***selectively amplifying*** nucleic acid sequences using ***multiple degenerate primers***. Thus, Navarro *et al.*, Kool, Oyama *et al.*, and Waggoner *et al.*, either alone or in combination, fail to disclose or suggest each and every element of claims 72 and 73. Accordingly, Navarro *et al.*, Kool, Oyama *et al.*, and Waggoner *et al.* do not make obvious claims 72 and 73. Applicants respectfully request withdrawal of these rejections.

A Credit Card Payment submitted via EFS WEB authorizing payment in the amount of $60.00, representing the extension of time fee for a small entity under 37 C.F.R. § 1.17(a)(1) and a Request For Extension of Time are enclosed. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

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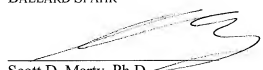

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